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10/789,835	02/27/2004	Todd A. Thompson	960296.00516	8254

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
05/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

Office Action Summary	Application No.	Applicant(s)	
	10/789,835	THOMPSON ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,8,9 and 11-24* is/are pending in the application.

4a) Of the above claim(s) *11-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 2/19/2009, are acknowledged and entered. Claims 1, 2, 5, 6, 8, 9, and 11-24 are presented for examination.

Claims 11-24 remain withdrawn from further consideration as being drawn to non-elected subject matter. Claims 1, 2, 5, 6, 8, and 9 are presently under examination and are the subject of this Office Action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/19/2009 has been entered.

Response to Arguments

Applicants' arguments, filed 2/19/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-2, 5-6, and 8-9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention regarding to whom or what the claimed compounds are being administered, is **withdrawn** in light of Applicant's amendments.

Claims 1, 5, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1, 5, and 8 recite the broad recitation of a compound having the structure recited in the instant claims, and the claims also recite "which compound specifically binds to androgen receptor" which is the narrower statement of the range/limitation. While one compound (i.e., PMCol) has been shown to bind to the androgen receptor, there is no evidence of record that other compounds having the formula recited in the instant claims specifically bind to the androgen receptor. As such, it is unclear whether recitation of "which compound specifically binds to androgen receptor" is intended to be merely descriptive of the compounds having the structure recited in the claims (i.e., non-limiting) or whether recitation of "which compound specifically binds to androgen receptor" is intended to define a sub-genus of the compounds recited in the instant claims.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-2 and 5-6 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the growth of androgen-dependent prostate cancer tumor cells in a human having androgen-dependent prostate cancer tumor cells, or delaying the progression of androgen-dependent prostate cancer in a human having androgen-dependent prostate cancer, does not reasonably provide enablement for inhibiting the growth of androgen-dependent prostate cancer tumor cells or delaying the progression of androgen-dependent prostate cancer, or preventing the recurrence of androgen-dependent prostate cancer in patients not diagnosed as being in need of such treatment (*i.e.*, prevention), is **withdrawn** in light of Applicant's amendments.

Claims 8-9 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the growth of androgen-dependent prostate cancer tumor cells in a human *having* androgen-dependent prostate cancer tumor cells, or delaying the progression of androgen-dependent prostate cancer in a human *having* androgen-dependent prostate cancer, does not reasonably provide enablement for preventing the recurrence of androgen-dependent prostate cancer in patients (*i.e.*, prevention). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

> in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

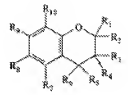
1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to preventing the recurrence of androgen-dependent prostate cancer in a human patient who has had or presently has androgen-dependent prostate cancer comprising administering a compound having the structure:

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".



wherein R_4 and R_5 are H; R_1, R_2, R_3, R_6, R_7, R_9 and R_{10} are independently an unsubstituted C_1-C_3 alkyl group; and wherein R_8 is an OH.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354), Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431), and Singh *et al.* (Endocrine-Related Cancer, 2006, vol. 13, pages 751-778).

Singh *et al.*, also cited for evidentiary purposes, review the mechanism of action of novel agents for prostate cancer chemoprevention. It is noted that "chemoprevention" as used in Singh *et al.* relates to prevention, suppression, and/or reversal of early and/or late stages of cancer growth (page 751). Optimal therapeutic response in prostate cancer patients has been

compounded by the problem of early diagnosis and with the emergence of androgen independence during commonly used anti-androgen therapy (Abstract). While many agents have been tested for chemoprevention in prostate cancer patients, there is no known agent that can prevent prostate cancer from occurring (pages 767-768).

This article plainly demonstrates that the art of preventing prostate cancer, particularly in humans, is extremely unpredictable.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 8) are broad, encompassing the prevention of androgen-dependent prostate cancer with a genus of compounds. Others, such as claim 9, are narrower, reciting a specific species of the claimed genus of compounds. All, however, are extremely broad insofar as they encompass the general prevention of androgen-dependent prostate cancer with the same compounds, only one of which has actually been tested for inhibiting the growth of existing prostate cancer tumors.

3. The amount of direction or guidance provided and the presence or absence of working examples

Firstly, it is noted that the present invention is based on the inventor's discovery that the chromanol-derived moiety of vitamin E possesses potent anti-androgenic activity in androgen-dependent cells (page 5, lines 11-13). In this regard, one compound was shown to have such activity. This compound, 2,2,5,7,8-pentamethyl-6-chromanol (PMCol), is a commercially available compound known for its antioxidant activity. Based on the anti-androgenic activity of this one compound *in vitro*, Applicant claims methods that encompass preventing androgen-dependent prostate cancer, in a human patient, with structurally related compounds.

The specification also provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to prevent androgen-dependent prostate cancer with the compounds encompassed by the claims, particularly in humans. The direction concerning treating prostate cancer is found in the specification at pages 37-44, which merely provides cellular assays for determining the cell growth inhibitory effect of one compound of the invention (PMCol). An *in vivo* assay for

determining the efficacy of the claimed compounds using an LNCaP xenograft model is provided at pages 50-52. No compounds were actually tested in this assay. Applicants describe formulations at pages 24-30. No doses useful in preventing prostate cancer in human patients are provided. Applicant asserts that "optimum effective amounts can be readily determined by one of ordinary skill in the art using routine experimentation" (page 24, lines 17-18). However, considering the broad scope of the claimed compounds, it would not be "routine" to determine effective doses of the claimed compounds in human patients.

As noted *supra*, there is both an *in vitro* cellular assay and an *in vivo* assay described at pages 37-44 and 50-52 (with no data in the *in vivo* assay) and it is unclear if these assays correlate to the prevention of prostate cancer in human patients. There is no working example of prevention of androgen-dependent prostate cancer in a human patient using the claimed compounds. Thus, there are no working examples correlating inhibition of the androgen receptor in cells with efficacy in the prevention of prostate cancer using the claimed compounds (*i.e.,* Applicant has not shown that inhibition of the androgen receptor with a compound of the invention correlates to *in vivo* prostate cancer prevention with the same compound).

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a prevention for androgen-dependent prostate cancer as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because PMCol has anti-androgenic activity *in vitro*, PMCol and compounds related to PMCol must therefore, *a priori*, be useful in the prevention of androgen-dependent prostate cancer in human patients. Determining if any particular claimed compound would prevent prostate cancer in humans,

would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants, especially in view of the fact that there is no known chemical agent that is effective in preventing prostate cancer *a priori*.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method comprising administering to a human subject an compound having the formula recited in the instant claims, "which compound specifically binds androgen receptor". The specification and claims lack written basis for the claimed compounds that specifically binds to the androgen receptor.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a genus of compounds having the formulas recited in the instant claims which compounds specifically bind to the androgen receptor.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical

properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

It is clear from the prior art that PMCol, which is the compound recited in claims 2, 6, and 9, has antioxidant activity and is a potent inhibitor of nuclear factor-kB activity. As such, PMCol does not appear to be a compound which specifically binds to the androgen receptor as recited in the instant claims. While Applicant has discovered that this compound is also an antagonist of the androgen receptor, this fact does not support Applicant's recitation of compounds which specifically bind to the androgen receptor because such specific binding implies that the compounds do not bind to any other receptors or biological targets in the body of a subject, which is clearly not the case.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a generic genus of compounds purported to specifically bind to androgen receptors and have anticancer activity. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-2 and 5-6 under 35 U.S.C. § 103(a) as being unpatentable over **Gunawardena *et al.*** (The Prostate, 2000, vol. 44, pages 287-295) in view of **Sheu *et al.*** (Life Sciences, 1999, vol. 65, pages 197-206) is **withdrawn** in light of Applicant's arguments. While the prior art suggests that vitamin E inhibits the growth of prostate cancer cells through apoptosis, there is no motivation in the prior art to cleave the phytyl group of vitamin E to arrive at the claimed compounds and reasonably expect such compounds to maintain efficacy, let alone inhibit androgen receptors.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614